

## REMARKS

This paper is being filed in response to the Office Action mailed March 10, 2005. Claims 1, 3, 5-10, 13, 15, 22, 27, 28, 34, 36, 40, 48, 53, and 60-83 have been amended and claims 84-96 have been added. Claims 1, 3, 5-10, 13, 15-58, and 60-96 are therefore pending. Support for the claim amendments can be found throughout the originally filed specification and drawings. For example, support for the amendment to claims 1, 5, and 22 for the recitation “acceptor variable framework region has at least one donor amino acid” is described *infra* at page 11 in the discussion relating to paragraph 4(i) rejection in the Office Action. Support for “chimeric” added to claim 27 is present on page 17, lines 20-21. Support for “a non-humanized antibody containing the variable domains of a 1A6 antibody” now recited in claims 5-10, and 74-83, is present in Example 1 (page 34) of the originally filed specification which describes the making of a 1A6 scFv having variable domains of 1A6. Support for new claim 84 is present, for example, in claim 1 and at page 14, lines 20-22. New claim 84 is broader than any of previously presented claims 1, 4, or 22, and claim 84 has not been added in response to any rejection or any assertion by the Patent Office relating to patentability. Accordingly, *Festo* has no applicability and the Doctrine of Equivalents is fully applicable to all aspects of the new claim 84 and the additional new claims. Support for new claim 92 is present, for example, at page 14, lines 18-20 of the original specification. Support for new claim 93-95 is present, for example, at page 14, lines 25-27. No new matter has been added, and entry of the amendments to the specification and claims is hereby requested.

### Regarding the Amendments to the Specification and Sequence Listing

The specification has been amended for clarity and to insert sequence identifiers (SEQ ID NOS) in accordance with the requirements for sequences under 37 C.F.R. §§1.821-1.825. A Substitute Sequence Listing, in Paper and Computer readable form, is submitted herewith. The Paper and Computer readable forms of the Substitute Sequence Listing are identical and do not add new matter. An executed statement under 37 C.F.R. §§1.821 to this effect is also submitted concurrently herewith. Thus, as the Substitute Sequence Listing does not add new matter, entry thereof is respectfully requested.

### Regarding the Claim Amendments

The amended and new claims are not narrowing, and the doctrine of equivalents is fully applicable to all aspects of the claim as amended. The amendments to claims 1, 3, 5-10, 15, 22,

28, 34, 36, 40, 48, 53, 60-83 and the addition of new claims 84-94 have not been for reasons relating to any rejection alleged herein, and instead been introduced for the purpose of covering commercial embodiments and facilitating prosecution. The claim amendments and new claims add no new matter and basis can be found in the specification throughout and in the claims as filed. It is respectfully submitted that the rejections of pending claims 1, 3, 5-10, 13, 15-58, and 60-94 are inapplicable to the claims as currently pending as discussed hereafter. It is further submitted that the rejections of formerly pending claims are inapplicable to the new claims.

*Drawings*

In response to the Office Action mailed March 10, 2005, Applicants hereby submit corrected formal drawings of Figures 3 and 5. In addition, corrected formal drawing of Figure 4 is also submitted herewith to correct a minor typographical error. No new matter has been added.

*Objection to the Disclosure*

The disclosure is objected to for alleged inconsistencies in the descriptions for Figure 1 and Figure 3. Amendments to paragraphs [0013] and [0016] of the Specification contain revised descriptions for Figure 1 and Figure 3. Accordingly, in view of these corrections, Applicants respectfully request that the objection be withdrawn.

**Rejections under 35 U.S.C. 112, second paragraph**

In paragraph 4, the Patent Office rejected claims 1, 3-10, 13, 15-57 and 60-83. The rejection by the Patent Office in paragraph 4(i) is respectfully traversed and Applicants request that this rejection be reconsidered and withdrawn. The Patent Office objected to the recitation of “non-human amino acid” and “human amino acid.” Applicants disagree. This is standard language used to reference interspecies amino acid positional substitutions and those in the art would find this language unambiguous when read in conjunction with the instant specification. Despite this proper language, in order to advance prosecution, in the claims as amended and the new claims, Applicants rewrote “non-human amino acids” and “human amino acids” to refer to an “acceptor variable framework region has at least one donor amino acid.” Support for Applicant’s recitation of “acceptor variable framework region” can be found at page 7, line 8 and page 34, lines 16-17. Support for Applicant’s recitation of “donor amino acid” can be found at page 7, lines 9-19. No substantive change is made by the recitation of acceptor for “human” and donor for “non-human,” nor has Applicant’s amendment in any way related to patentability, as

the claims were and are clear both prior to and after the change in language. This terminology conforms with the terminology used to describe the amino acids in the humanized antibodies of the present invention in the specification, and in the art.

The rejections in paragraphs 4(iii), 4(iii)(a) and 4(iii)(b) are respectfully traversed and Applicants request that this rejection be reconsidered and withdrawn. With regard to 4(iii), with no admission as to the propriety of the alleged rejection, claims 60-62 have been amended to recite that each identifies the range of donor amino acids found in the variable framework region of the humanized antibody. As previously presented and as amended, these claims clearly state that the human variable framework region of a humanized antibody contain a certain number of amino acids from the CDR donor antibody sequence. The inclusion of amino acids from the CDR donor antibody sequence in the human variable framework region of a humanized antibody is disclosed in the instant specification. See for example, page 1, lines 19-35 which report:

CDR's, also called hypervariable regions, are present in immunoglobulin light and heavy chains and are flanked by "framework" regions. CDR grafting was first described in Jones et al. ((1986) *Nature* 321:522-525). In this and later publications, the CDRs of three mouse antibodies were grafted onto the variable domain frameworks of the human immunoglobulin NEW (V<sub>H</sub>) and REI (V<sub>L</sub>). The resulting humanized antibodies had the same antigen specificity and a similar affinity as the parental murine monoclonal antibody (mAb) (Jones et al. *supra*; Verhoeven et al. (1988) *Science* 239:1534-1536; Riechmann et al. (1988) *Nature* 332:323-327; U.S. Pat. No. 5,225,539).

CDR grafting has been described by Queen and coworkers who reported the humanization of four murine monoclonal antibodies (Queen et al. (1989) *Proc. Natl. Acad. Sci. USA* 86:10029-10033; Co et al. (1991) *Proc. Natl. Acad. Sci. USA* 88:2869-2873; Co et al. (1992) *J. Immunol.* 148:1149-1154; and U.S. Pat. Nos. 5,585,089; 5,693,761; and 5,693,762). Murine residues were inserted in the human framework in order to maintain affinity and, in each case the original antigen specificity was maintained. The affinities of the humanized antibodies ranged from 1/3 to 3 times of the parental unmodified murine antibodies.

With respect paragraph 4(iii)(a), the Patent Office alleges that a humanized antibody consists of a donor non-human CDR and an acceptor human variable framework region. The Patent Office further alleges that if a humanized antibody of Applicants' claimed invention contains amino acids from the CDR donor antibody's variable framework region, then "it is unclear as to what is encompassed by Applicant's assertion of 'humanized' antibody." The instant claims are not limited to having identity with a human framework. Certain claims of the

instant application include an antibody having amino acid substitutions in the human framework, and these substitution may be made with reference to a human consensus variable framework region sequence. For example, claim 1 includes an antibody having a V<sub>L</sub> and V<sub>L</sub> region comprising SEQ ID NO:5 and SEQ ID NO: 7 wherein an acceptor variable framework region of one or both of the preceding has at least one non-human donor amino acid. Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

With respect to paragraph 4(iii)(b), the Patent Office alleges that:

“the claims are directed to derivatives of the claimed humanized antibody, aside from the subsequence claimed. If this is Applicant’s intentions, then it is not readily apparent in the claims. Additionally, similar to the analysis provided above, the claimed invention is directed at a humanized antibody; thus, implicating the presence of a human framework. Ergo, it is unclear as to which amino acid(s) should be substituted and amino acid(s) that can be used to replace the substituted amino acids; since both are based upon a human consensus variable framework region sequence.”

Guidance regarding the substitution of amino acids in an acceptor variable framework region with donor non-human amino acids is provided throughout the specification and in Example 1 of the instant application, for example. In this Example, Applicants describe one embodiment of creation of a claimed humanized antibody. Applicants compared the donor 1A6 heavy chain variable framework region sequence to that of the human VH III consensus sequence, which share 56 of the 82 amino acids in the heavy chain framework. (Application page 34, lines 22-24). A similar comparison for the light chain found 52 of 81 amino acids shared between the human Kappa I consensus sequence and the donor 1A6 light chain variable framework region sequence. (Application page 34, lines 24-26). A majority of the different amino acids for both the light and heavy chain were found to be located on the surface of the antibody, or residues with similar characteristics. (Application page 34, lines 27-30). The remaining six amino acids, located at positions VH 37, 69, 71, 73 and 94 and VL 49, belong to the “Vernier” zone that form a layer underlying the CDRs and may impact on the structure of CDRs and the affinity of the antibody. (Application page 35, lines 1-4). Applicants describe the selection of residues at these positions based on molecular model building. (Application page 35, lines 4-5; Fig. 2). The selection of amino acids for the “Vernier” zone is described, for example, on page 35 through page 36 of the Application. Additional disclosure is found in Example 2. Applicants have provided sufficient disclosure for those in the art to determine which amino acids in the human acceptor variable framework region they wish to replace by the corresponding amino acid at the

same position in the variable framework region of the CDR donor amino acid sequence. As such, Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

The rejection by the Patent Office in paragraph 4(iv) is respectfully traversed and Applicants request that the rejections be reconsidered and withdrawn. In rejecting claims 63-83, the Patent Office alleges that “it is unclear what Applicant regards as the ‘substituted’ and ‘unsubstituted’ antibody.” Applicants disagree. The use of “substituted” is unambiguous, and would be clear to one of skill in the art when read with an understanding of the instant specification. However, in order to expedite prosecution without and admission as to the propriety of this rejection, Applicants have amended the claims to read “an acceptor variable framework region of the humanized antibody has at least one donor non-human amino acid.” Accordingly, Applicants request that the rejection under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

The rejection by the Patent Office in paragraph 4(v) is respectfully traversed. There is nothing confusing about the meaning or “inhibiting HRV progression.” HRV progression, like most viral progression is well understood in the art. For instance, in Weltzin and Monath, the authors identify that viral progression occurs as virus particles are released from infected cells to then infect new cells. Weltzin and Monath, *Clinical Microbiology*, Vol. 12, p. 383-93 (July, 1999). Rubio *et al.*, (2001) discloses the measurement of viral progression in Figure 6(C). Rubio *et al.*, *J. Virology*, Vol. 75, p. 11573-82 (2001). In this figure, Rubio *et al.*, disclose the progression of viral variants MVMi and MVMi-NSp in culture. Rubio *et al.*, (2005) discloses the measurement of viral progression in Figure 2(C), titled “Viral Progression.” Rubio *et al.*, *J. Virology*, Vol. 79, p. 11280-90 (2005). As such, the rejection of claims 48-52 has no merit and Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

Applicants request that the rejection of claims 1, 3-10, 13, 15-57 and 60-83 by the Patent Office in paragraph 4(vi) be reconsidered and withdrawn as inappropriate given that the claims are clear. The claimed antibody, or subsequence thereof, can include fragments that comprise all of SEQ ID NOs: 5 and 7, or part of each. However, whatever the subsequence thereof is, the antibodies bind ICAM-1. Thus, what constitutes a subsequence is clear from the language of the claims on their face, it is a fragment of a humanized antibody comprising that portion of SEQ ID

NOs: 5 and 7 that binds ICAM-1. Further, the instant Application, for example on page 10, lines 8-15, and Example 2 provide descriptions of specific subsequences such as Fab, Fab', (Fab')<sub>2</sub>, Fv, or single chain antibody fragment (e.g. scFv). Each of these is well known in the art and their preparation is within the knowledge of one of skill. As such, the rejection is without merit and Applicants respectfully request that the rejection under 35 U.S.C. §112, second paragraph, be withdrawn.

### **Rejections under 35 U.S.C. 112, first paragraph**

In paragraph 5 of the March 10, 2005 Office Action, claims 1, 4, 16-22, 25-57 and 60-83 were rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the written description requirement. The Patent Office asserts:

The claims do not require that the fragments possess any particular distinguishing feature, biological activity, or conserved structure.....The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. ....In this case the only factor present in the claims is the fragments are derived from HumB. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus, any fragments that can be derived from HumB.(page 7 of Office Action, emphasis added)

Applicants respectfully disagree and traverse this rejection. As is discussed below, the Patent Office is incorrect in asserting that only one of the above factors is present. As a threshold matter, Applicants would like to clarify that the legal standard for determining whether a claim meets the requirements of 35 U.S.C. 112, first paragraph requires more than an analysis of the claim at issue. The CCPA has made the following remarks regarding this standard:

[I] t is well settled that the disclosure of an applications not only what is expressly set forth in words or drawings, but what would be understood by persons skilled in the art. As was said in *Webster Loom Co. v. Higgins et al.*, 105 U.S. 580, 586, the applicant “may begin at the point where his invention begins, and describe what he has made that is new and what it replaces of the old. That which is common and well known is as if it were written out of the patent and delineated in the drawings”. *In re Howarth*, 654 F.2d 103, 210 USPQ 689, 692 (C.C.P.A.) (quoting *In re Chilowsky*, 229 F.2d 457, 460, 108 USPQ 321, 324 (C.C.P.A. 1956)).

Thus, the claims must be read in light of the specification, and with the knowledge and understanding of one of skill in the art.

A humanized antibody that binds ICAM-1, comprising SEQ ID NO:5 and 7, or a subsequence thereof, wherein an acceptor variable framework region of the humanized antibody has at least one non-human donor amino acid.” With respect to a “complete or partial structure”, the instant specification teaches that a “subsequence” can refer to, for example, single chain, Fab, Fab' or (Fab)<sub>2</sub> fragments. (see page 10, lines 8-9). Claim 1 explicitly recites SEQ ID NO:5 and SEQ ID NO:7, which are sequences for the V<sub>H</sub> and V<sub>L</sub> domains of the humanized antibody. Subsequences of SEQ ID NO:5 and SEQ ID NO:7 are inherently present in the disclosed sequences. Additional specific sequences are provided throughout the specification (see page 10, lines 14-18 of the originally filed specification). A tertiary structure model for a humanized antibody is provided in Figures 2A, 2B, and 2C of the instant application, and structural significance of particular amino acid residues is discussed in Example 1 (see page 35-36). Applicants respectfully submit that, from these primary amino acid sequences and subsequences (e.g. SEQ ID NO:5 and SEQ ID NO:7) and the tertiary structures described in Figure 2, one of skill in the art could readily determine the structure of a protein having these primary sequences or subsequences thereof without undue experimentation.

Applicants also disagree with the alleged lack of teaching regarding “physical or chemical properties” and “characteristics, structure/function correlation.” Contrary to the position asserted by the Patent Office (see page 9, last paragraph of point 5), claim 1 recites that the antibody binds to ICAM-1. Such binding is a well defined physical property, and it provides a very specific characterization of a structure/function correlation. In support of this teaching, the specification also teaches that an antibody subsequence will retain the ability to selectively bind an antigen even though the binding affinity of the subsequence may be greater or less than the binding affinity of the full length antibody. (See page 10, lines 8-18). The Examiner’s attention is also drawn to Example 4, which teaches an ELISA assay that was used to measure the binding affinity of antibodies to ICAM-1. Applicants respectfully submit that the method described in Example 4 taken in conjunction with the teachings of the instant specification, would clearly allow one of skill in the art to practice the full breadth of the humanized antibody embodied in claim 1 without any undue experimentation.

The Patent Office is reminded that not all species of subsequences of the claimed antibodies need be disclosed to meet the legal requirements of 35 U.S.C. 112, first paragraph. The Courts have repeatedly held that “every species in a genus need not be described in order

that a genus meet the written description requirement.” *Reagents of the Univ. Calif. v. Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

In summary, claim 1 and all claims that depend therefrom are supported in a manner that the Patent Office asserts is used in making such a determination. Accordingly, Applicants request that the rejection of claims 1, 4, 16-22, 25-57 and 60-83 under 35 U.S.C. 112, first paragraph, be reconsidered and withdrawn.

Claims 1, 3-10, 13, 15-57 and 63-83 were rejected under 35 U.S.C. 112, first paragraph, in paragraph 6 of the Office Action as allegedly being indefinite. Again, Applicants request that this rejection be reconsidered and withdrawn. Amended claim 1 is broader in scope and the amendment was not made for any reason relating to the patentability. Regarding the alleged lack of support for the added limitation “wherein a variable framework region of the humanized antibody has had at least one non-human amino acid substituted with a human amino acid”, this assertion is discussed above. The alleged rejection of claims 71 and 82 is also inapplicable. Accordingly, Applicants request that all rejections in paragraph 6 of the Office Action be reconsidered and withdrawn.

In paragraph 7 of the Office Action, claims 1, 4, 16-22, 25-27, and 60-83 were rejected under 35 U.S.C. 112, first paragraph. The Office Action asserts that the specification does not reasonably provide enablement for subsequences of HumB that does not bind to ICAM-1. Applicants do not understand this rejection because the pending claims are directed to humanized antibodies that bind to ICAM-1. Applicants request that the Patent Office clarify this rejection, or reconsider and withdraw the rejection.

In paragraph 8 of the Office Action, claims 5-19, 13, and 16-57 were rejected under 35 U.S.C. 112, first paragraph. Applicants traverse this rejection. The 2003 Charles *et al.* publication does not support the assertion of the Patent Office that *in vitro* results are not predictive of *in vivo* results. The excerpt of Charles *et al.* relied upon by the Patent Office merely states:

A receptor-blocking approach has shown that anti-ICAM-1 monoclonal antibody (MAb) 1A6 prevents HRV infection of cells *in vitro* (3). In human clinical trials, the antibody diminished cold symptoms but failed to prevent onset of the disease (8).

The excerpt provided above reports that *in vitro* results were predictive of successful treatment with a antibody for successfully diminishing cold symptoms *in vivo*. From the above passage, it is clear that Charles *et al.* does not support a conclusion that the *in vitro* data fail to support the

antibodies covered in claim 5. Specifically, the binding studies in Example 4 and the HeLa cell data presented in Example 5 of the instant application are, in contrast to the assertion of the Patent Office, predictive of successful treatment of HRV induced cold symptoms *in vivo* with humanized antibodies. The rationale asserted by the Patent Office is also inconsistent with the scope of claim 5, which is directed to a humanized antibody that binds ICAM-1 and inhibits human rhinovirus (HRV) infection of cells expressing ICAM-1 and has a protective efficacy against HRV that is greater than the non-humanized antibody containing the variable domains of mouse monoclonal antibody 1A6. The instant claims are not limited to preventing the onset of a cold. Applicants Response filed November 29, 2004 (see page 23) also provides numerous peer review publications that support the general acknowledgment in the art that the use of a HeLa cell model system is well recognized as predictive of therapies from HRV infection *in vivo*.

#### **Rejection Under 35 U.S.C. §102 (b)**

##### **Pedersen *et al.***

Claims 1 and 22 have been rejected under 35 U.S.C. 102(b) as allegedly anticipated by Pedersen *et al.* (US Patent No. 5,639,641), on the assertion that Pedersen *et al.* discloses a sequence, SEQ ID NOS: 497, which is Arg Ala Ser Gln Ser Ile Ser Asn Asn Leu His. It is alleged that “SEQ ID NO: 497 has a 100% identity to a fragment of the claimed antibody and subsequences thereof. Ergo, Pedersen *et al.* anticipates the claimed invention.” This rejection is traversed, and Applicants request that the rejection be reconsidered and withdrawn.

The claims currently pending in the instant application all claim a humanized antibody comprising SEQ ID NOs: 5 and 7, or subsequences thereof. All Pedersen *et al.* discloses is an eleven amino acid sequence that corresponds to amino acid residues 24-34 of SEQ ID NO 7. Thus, as a matter of law, neither claim 1 nor claim 22 read on this sequence and thus cannot be anticipated by it.

Additionally, contrary to the Patent Office’s assertion, SEQ ID NO:497 of Pederson does not have a 100% homology with SEQ ID NO:7 of the instant application. The amino acid residue at position 30, which in SEQ ID NO:7 is a Ser, is a Gly in SEQ ID NO:497 of Pederson *et al.*. As such, it is not a match. All Pederson *et al.* discloses is a short sequence comprising barely 10% of SEQ ID NO:7, and this short sequence is not identical to SEQ ID NO:7.

Pederson *et al.* additionally fails to teach or suggest an antibody comprising SEQ ID NO:5 (claims 1, 4, 22, and 84), a subsequence of an antibody comprising SEQ ID NO:5 and SEQ ID NO: 7 (claims 86-89), or an antibody or subsequence of an antibody comprising SEQ ID NO:5 and SEQ ID NO: 7 of subsequences thereof (claim 1).

Moreover, Pederson *et al.* fails to report an antibody that binds ICAM-1 (claims 1, 4, 22, and 85), and accordingly it fails to teach a humanized antibody that bind ICAM-1 with a significantly enhances binding affinity as compared to one that is not humanized (claims 6-10, claims 64-83). In fact, Pederson *et al.* in no way even mentions ICAM-1.

Further, Pederson *et al.* fails to teach or suggest a multimeric antibody (claims 17-21, and 91).

Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration. Plainly Pederson is of no consequence in this regard vis a vis the claims of the instant application.

#### **Rejection Under 35 U.S.C. §103(a)**

##### **Colonna in view of Padlan**

Claims 1, 3-4 were rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Colonna *et al.* and Padlan. The rejection is respectfully traversed.

The Patent Office acknowledges that neither of Colonna *et al.* or Padlan suggest a humanized antibody in which a variable framework region of the humanized antibody has had one or more non-human amino acids substituted in place of human amino acids. See page 10 of the Office Action, which states:

While applicant is correct to note that neither suggests a humanized antibody in which a variable framework region of the humanized antibody has had one or more non-human amino acids substituted with a human amino acid, however, the submission cannot be considered on its merits because it is unclear as to what is intended by Applicant with the limitation, ...humanized antibody has had one or more non-human amino acids substituted with a human amino acid. (emphasis added)

Applicants request that the Patent Office reconsider its position that these patentably distinct differences in light of the above discussion under Section 112, and request that the rejection of claims 1, 3-4 over Colonna *et al.* and Padlan (1991) (1994) be reconsidered and

withdrawn. However, for further clarification the impropriety of the rejection under 35 U.S.C. §103 is described in greater detail below.

#### **Colonna *et al.***

Table 3 (page 11) of Colonna *et al.* shows the amino acid sequences of the heavy chain and light chain variable regions of the 1A6 monoclonal antibody. No attempts to humanize the mouse IgG-1 monoclonal antibody sequences were reported in Colonna *et al.* Accordingly, Colonna *et al.* fails to teach an antibody with human framework sequences. As such, Colonna *et al.* fails to disclose a humanized antibody where an acceptor variable framework region of the humanized antibody has at least one non-human donor amino acid (claim 1 of the instant application).

Colonna *et al.* fails to teach or suggest an antibody comprising SEQ ID NO:5 and SEQ ID NO: 7 (claim 84), a subsequence of an antibody comprising SEQ ID NO:5 and SEQ ID NO: 7 (claims 86-89), or an antibody or subsequence of an antibody comprising SEQ ID NO:5 and SEQ ID NO: 7 of subsequences thereof (claim 1).

A still further distinction is that Colonna *et al.* fails to teach or suggest a multeric antibody (claims 17-21, and 91).

In summary, Colonna *et al.* fails to disclose or in any way suggest a antibody of the instant invention. Notwithstanding the deficiencies of Colonna *et al.*, neither Padlan (1991) or Padlan (1994) complete a *prima facie* case. In addition to its inadequacies, as is discussed below, Colonna *et al.* is not properly combinable with either Padlan (1991) or Padlan (1994).

#### **Padlan (1991)**

Padlan (1991) references a method to “humanize” an antibody, but teaches away from Applicants’ inventions. Rather than grafting the non-human donor CDRs into human acceptor variable framework region, Padlan refers to identification of particular amino acids in the murine donor variable framework region that lie on the surface of the antibody that should be changed to the corresponding human acceptor variable framework region amino acid located at the same location. As a result, the number of amino acids changed in the murine donor variable framework region to the corresponding human acceptor amino acid at the same location is small. As stated by Padlan,

“On the basis of this proposal, the number of residues in a mouse framework that would need to be replaced to “humanize” it can be determined for each representative mouse variable domain. This number is found to range from 7 to 16, when the mouse sequences

are correlated with the most frequently occurring residues in the human variable subgroups, residues in the human variable domain subgroups, and from 6 to 15 when they are compared with the human sequences to which they are most similar.” (Padlan (1991) Page 495)

### **Padlan (1994)**

Padlan (1994) is a 48 page review article entitled “Anatomy of the Antibody Molecule”. The abstract of the publication states that “[T]he structures of the various regions of an antibody molecule are analysed and correlated with biological function. The structural features which relate to potential applications are detailed”. It is not clear what the Patent Office is relying upon in this article for the basis of the rejections under 35 U.S.C. §103. However, Padlan 1994 is analogous to Padlan 1991 regarding the teaching of retaining donor-antibody (non-human) framework sequences in the humanized antibodies to preserve antigen binding activity. For example, Padlan 1994 reports “some framework residues from the original antibody, those which influence the structure of the combining site, also need to be preserved.” (page 201, second column, first paragraph).

A still further deficiency regarding the notion of combining Colonna *et al.* with Padlan is that there is no disclosure to show that an antibody using the sequence of Colonna *et al.* and the methods of Padlan would have an affinity for ICAM-1 that is equivalent to the humanized antibodies claimed in the instant application. It has been reported that some humanization procedures would be expected to lead to a complete loss of binding affinity (see Luo G.X. *et al.*, Humanization of an anti-ICAM-1 antibody with over 50-fold affinity and functional improvement, *J.Immunol. Meth.* 275:31-40, 32 (2003), copy will be provided under separate cover). The Luo *et al.* publication describes the work of Perlan Therapeutics, assignee of the instant application. For additional examples of the binding affinity of humanized antibodies claimed in the instant application, the Examiner is directed to page 47, lines 20-30 and Table 4 of the filed application, which report that the humanized scFv proteins of the invention exhibited greater than 10 times higher binding affinity for ICAM-1 than the parental mouse scFv. These binding affinities would not be expected from the teaching of Colonna *et al.* or Padlan. For this reason alone, one of skill in the art would not have a reasonable expectation of success that a combination of Colonna *et al.* and Padlan would successfully arrive at the claimed humanized antibodies.

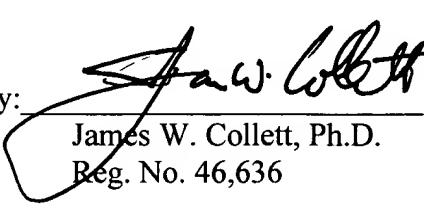
It is well established that "To establish a *prima facie* case, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference or references, when combined, must teach or suggest all the claim limitations. MPEP 706.02(j), citing, *In re Vaeck*, 947 F.2d 488, 20 USPQ 2d 1438 (Fed. Cir. 1991) (emphasis added). Applying the law to the current facts, Applicants respectfully submit that the Patent Office has failed to complete a *prima facie* case as required under 35 U.S.C. §103 because it has failed to establish appropriate suggestion or motivation, a reasonable expectation of success, and that a combination of the references teach or suggest all the claim limitations. Accordingly, Applicant request that the rejections under 35 U.S.C. §103 be reconsidered and withdrawn.

### CONCLUSIONS

For the reasons described and supported above, Applicants respectfully submit that all pending claims are now in condition for allowance. That said, should any issues or questions remain, the Examiner is encouraged to telephone the undersigned at (619) 744-2240 so that they may be promptly resolved. In the unlikely event the transmittal letter is separated from this document and the Office determines that an extension and/or other relief is required, Applicants petition for any required relief, including extensions of time, and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to the credit card disclosed in form PTO-2038 filed with this document.

Respectfully submitted,

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